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Clinical Investigation

Postmastectomy Radiation in Breast Cancer Patients With Pathologically Positive Lymph Nodes After Neoadjuvant Chemotherapy: Usage Rates and Survival Trends

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Summary

We analyzed postmastectomy radiotherapy (PMRT) usage and its association with overall survival in breast cancer patients with pathologically positive lymph nodes after neoadjuvant chemotherapy using the National Cancer Database, including 29,270 patients. PMRT was underused, in particular, among ypN2 (68.4%) and ypN3 (67.0%) patients. The 5-year overall survival rates were greater in ypN3 patients receiving

Purpose: To analyze postmastectomy radiation therapy (PMRT) usage and its association with overall survival (OS) in breast cancer patients with pathologically positive lymph nodes after neoadjuvant chemotherapy (NAC).

Methods and Materials: Using the National Cancer Database, we identified women with nonmetastatic breast cancer diagnosed from 2004 to 2013 who had received NAC and undergone mastectomy with macroscopic pathologically positive lymph nodes. Joinpoint regression models were used to assess temporal trends in annual PMRT usage. Multivariable regression models were used to identify factors associated with PMRT use. A time-dependent Cox model was used to evaluate the predictors of mortality.

Results: The study included 29,270 patients, of whom 62.5% received PMRT. PMRT was markedly underused among all nodal subgroups, in particular, among ypN2 (68.4%) and ypN3 (67.0%) patients. Hispanic patients and those with Medicaid or Medicare insurance were less likely to receive PMRT than were non-Hispanics and patients with other insurance carriers. The adjusted 5-year OS rates were similar in ypN1 and ypN2 patients with or without PMRT but were significantly greater in ypN3 patients receiving PMRT (66% vs 63%; $P = .042$). On multivariable analysis, PMRT was associated with improved survival only among ypN3 patients after

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PMRT (66% vs 63%; $P = .042$). PMRT was associated with improved survival only among ypN3 patients (multivariable hazard ratio 0.85; 95% confidence interval 0.74-0.97).

adjusting for patient, facility, and tumor variables (multivariable hazard ratio 0.85; 95% confidence interval 0.74-0.97).

Conclusions: A considerable portion of breast cancer patients with advanced residual nodal disease after NAC did not receive appropriate adjuvant radiation. We also found socioeconomic disparities in national PMRT practice patterns. Patients with ypN3 disease might derive a survival benefit from PMRT.

Introduction

Neoadjuvant chemotherapy (NAC) is commonly used for patients with locally advanced breast cancer. The potential benefits of NAC include pathologic downstaging to facilitate breast-conserving surgery, avoiding delays in systemic therapy due to postoperative wound-healing complications, and upfront treatment of micrometastatic disease (1, 2). Another possible advantage, currently under investigation in national clinical trials, is the opportunity to limit subsequent locoregional therapy, depending on the initial clinical stage and the tumor's response to treatment.

Although the benefits of postmastectomy radiation therapy (PMRT) after upfront surgical resection with or without adjuvant chemotherapy have been well-established (3-5), the role of PMRT after NAC is more controversial owing to a lack of randomized data in this setting. A pooled analysis of the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 studies and several retrospective series have attempted to address the benefits of PMRT after NAC. The available data suggest that both the prechemotherapy clinical stage and the post-chemotherapy pathologic stage predict for locoregional recurrence (LRR) and should inform adjuvant locoregional management (6-9).

In the absence of compelling randomized evidence to guide locoregional therapy, however, the variation in national PMRT practice patterns after NAC is likely wide. We analyzed the National Cancer Database (NCDB) to evaluate the recent trends in PMRT usage and assess the effect of PMRT on overall survival (OS) in patients with pathologically positive lymph nodes after NAC.

Methods and Materials

Data source

The NCDB, a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society (ACS), is a registry comprising data from >1500 hospitals with CoC-accredited cancer programs in the United States and includes approximately 70% of all newly diagnosed cases of cancer. The data are collected by participating cancer programs' registries and include patient characteristics, cancer staging, tumor histologic characteristics, type of first-course treatment administered, and outcomes. The NCDB has previously been described in detail (10). The present study used de-identified data and was granted human research exemption from the Icahn School of Medicine at Mount Sinai institutional review board. The ACS and CoC have not verified and are not responsible for the analytic or statistical method used or the conclusions drawn from these data.

Patient selection

The NCDB was queried to identify patients with invasive, nonmetastatic breast cancer diagnosed from 2004 to 2013 who had received NAC, underwent mastectomy, and had macroscopic pathologically positive lymph nodes. NAC was defined by an interval from the initiation of chemotherapy to surgery of $\geq$80 days and $\leq$270 days. Patients with clinical or pathologic evidence of metastatic disease were excluded, as were patients with bilateral or inflammatory breast cancer. Patients who received neoadjuvant hormonal therapy, neoadjuvant radiation therapy, and/or intraoperative chemotherapy were also excluded. Finally, patients who did not receive any treatment at the reporting facility were excluded, as recommended by the NCDB.

PMRT was defined as the delivery of $\geq$45 Gy of external beam radiation therapy to the chest wall with or without regional lymph node irradiation. Patients who received an undefined radiation dose or those coded as receiving a dose <45 Gy, which likely represented palliative treatment, were included in the no-PMRT group. To analyze trends in PMRT usage, we used the data from 2004 to 2013. The survival analyses were limited to data from 2004 to 2008 to ensure a minimum follow-up period of 5 years from diagnosis and to limit censoring bias.

Predictor variables

We considered patient, facility, and tumor level variables in the analyses. The patient-level variables included age, race, ethnicity, insurance status, median income quartile by zip code, and the Charlson-Deyo comorbidity score (truncated by the NCDB into 0, 1, and $\geq$2). The facility-level variables included the type of facility, assigned by the CoC according to the annual caseload and available services, distance from patient area of residence to the reporting facility, and geographical region (corresponding to the US census divisions). Tumor-specific variables included

pathologic stage (using the American Joint Committee on Cancer/Union for International Cancer Control TNM system), laterality, grade, surgical margin status, number of regional lymph nodes examined, receipt of hormonal therapy, and presence of immediate breast reconstruction.

Missing data

The missing data for the predictor variables were managed by multiple imputation using chained equations (11). Among these variables, facility type and geographical region had the greatest frequencies of missing data at 14.9%, followed by grade (9.3%), ethnicity (5.7%), pathologic T category (4.4%), hormonal therapy (3.9%), number of regional lymph nodes examined (1.8%), and surgical margin status (1.8%). All other variables were missing for $<1\%$ of patients. Data appeared to be missing at random (ie, missing information was related only to observed variables), rather than missing completely at random (ie, missing information was unrelated to the observed and unobserved data). Multiple imputation has been shown to be superior regarding analytic bias compared with alternative approaches, such as complete case analysis, when data are missing at random (12). Additionally, because 41.6% of patients had ≥ 1 prognostic variable missing, a complete case analysis would likely have resulted in a substantial loss of statistical power.

The sequential regression imputation method, referred to as chained equations, was implemented using the IVEware software system (11). The process begins for each variable with the missing values imputed using a univariable logistic, ordinal, multinomial logistic, or predictive mean matching regression model, conditional on all other variables. The process cycles iteratively through the variables containing missing values until the procedure is stable. We performed 10 repetitions of this cycle to generate 15 imputed data sets.

Statistical analysis

The primary objectives of the present study were to identify the trends in PMRT usage from 2004 to 2013 and to compare OS between the patients who received PMRT and those who did not. OS was measured from the date of diagnosis to the date of death from any cause. The secondary objectives were to determine the effect of PMRT on OS in clinically relevant patient subsets. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, NC) and R, version 3.2.1 (R Project for Statistical Computing, Vienna, Austria). Hypothesis testing was 2-sided and conducted at the 5% level of significance.

Trends in PMRT usage

We used the Joinpoint Regression Program, version 4.2.0.2, developed by the US National Cancer Institute, to assess temporal trends in the annual PMRT usage rates for all patients combined and stratified by age, race, and facility location. The Joinpoint software fits the simplest model to describe the usage rate trend data, starting with a straight line (0 joinpoints) and then adding more joinpoints to determine whether multiple connecting lines would better describe the data points. The software identifies the years when the annual percentage of change trends appeared to shift upward or downward and whether these trends were statistically significant.

Patient, facility, and tumor variables stratified by treatment group

The patients who received PMRT and those who did not (no-PMRT group) were compared with respect to the patient-, facility-, and tumor-level variables previously outlined. Continuous variables are reported as the median and range and nominal variables as numbers and percentages. Multivariable log-binomial regression models were used to estimate the adjusted prevalence ratios and 95% confidence intervals (CIs) to evaluate the association between each variable and treatment status while adjusting for all other variables.

Survival modeling

Because the PMRT initiation dates varied among the patients, hazard ratios (HRs) and 95% CIs were estimated with a time-dependent Cox regression model (TDCRM), adjusting for all patient-, facility-, and tumor-level variables. In the TDCRM model, PMRT exposure was treated as a time-dependent variable with patients coded as having received no PMRT before radiation therapy initiation, then recoded to PMRT on the date when radiation therapy was initiated. For the patients who never received radiation, coding as no PMRT was applied throughout. Using this method to address the immortal time bias, which is introduced by the variation in the timing of PMRT initiation, the effect estimate for PMRT was less prone to overestimation (13).

In addition, a landmark analysis was performed that only included patients who were alive 12 months after diagnosis. The conventional Cox proportional hazards (CPH) model was used to estimate the HRs and 95% CIs for the landmark data set. This model was used to generate 2- and 5-year OS estimates and corresponding 95% CIs. The landmark analysis served as a sensitivity analysis to the time-dependent Cox regression modeling approach, both of which were used to address the issue of immortal time bias.

To account for the multiple imputation of missing data, Cox regression (for time-dependent and landmark analyses) was performed on each of the 15 imputed data sets, and estimates of the corresponding HRs and 95% CIs were then appropriately combined using the MIANALYZE procedure in SAS (14, 15). Finally, we assessed the heterogeneity of treatment effects stratified by nodal stage using subgroup analyses in the time-dependent and landmark models.

Table 1 Baseline patient, facility, and disease characteristics stratified by PMRT receipt and factors affecting treatment selection

Characteristic	PMRT		Multivariable prevalence ratio*	95% CI	*P* value
	No (n = 10,986)	Yes (n = 18,284)			
Age (y)					
≤50	5176 (36.8)	8873 (63.2)		Reference	
>50	5810 (38.2)	9411 (61.8)	0.994	0.979-1.009	.474
Median	51	51			
Range	20-90	19-90			
Race					
Missing	120 (41.0)	173 (59.0)			
White	8382 (36.9)	14,343 (63.1)		Reference	
Black	1997 (40.0)	2996 (60.0)	1.001	0.980-1.023	.909
Other	487 (38.7)	772 (61.3)	0.985	0.948-1.024	.446
Hispanic ethnicity					
Missing	647 (38.8)	1021 (61.2)			
No	9362 (36.9)	15,975 (63.1)		Reference	
Yes	977 (43.1)	1288 (56.9)	0.959	0.930-0.989	.007
Charlson-Deyo comorbidity score					
0	9620 (37.2)	16,242 (62.8)		Reference	
1	1131 (39.0)	1771 (61.0)	0.984	0.961-1.008	.198
≥2	235 (46.4)	271 (53.6)	0.923	0.868-0.982	.011
Primary payer					
Missing	205 (46.6)	235 (53.4)			
Not insured	501 (37.3)	842 (62.7)		Reference	
Private insurance/managed care	6880 (36.2)	12,106 (63.8)	1.003	0.969-1.038	.882
Medicaid/Medicare	3276 (40.1)	4887 (59.9)	0.962	0.929-0.997	.034
Other government insurance	124 (36.7)	214 (63.3)	0.954	0.883-1.031	.230
Median income quartile by zip code					
Missing	173 (44.6)	215 (55.4)			
<$38,000	2052 (40.0)	3079 (60.0)		Reference	
$38,000-$47,999	2309 (37.0)	3927 (63.0)	1.008	0.984-1.032	.522
$48,000-$62,999	2849 (37.4)	4762 (62.6)	0.989	0.966-1.013	.365
≥$63,000	3603 (36.4)	6301 (63.6)	0.987	0.964-1.011	.280
Distance from reporting facility (miles)					
Missing	164 (44.9)	201 (55.1)			
≤50	9709 (36.5)	16,887 (63.5)		Reference	
>50	1113 (48.2)	1196 (51.8)	0.903	0.876-0.931	<.001
Median	10.4	9.1			
Range	0-3800	0-3692			
Facility type					
Missing	1636 (37.5)	2728 (62.5)			
Community	906 (38.8)	1428 (61.2)		Reference	
Comprehensive	4331 (37.4)	7257 (62.6)	1.027	1.000-1.054	.050
Academic	4102 (37.5)	6836 (62.5)	1.031	1.005-1.059	.022
Other	11 (23.9)	35 (76.1)	1.102	0.905-1.342	.332
Facility location					
Missing	1636 (37.5)	2728 (62.5)			
Northeast	1595 (35.2)	2933 (64.8)		Reference	
South	4426 (42.6)	5972 (57.4)	0.955	0.935-0.976	.001
Central	1892 (30.5)	4322 (69.6)	1.032	1.010-1.055	.004
West	1437 (38.2)	2329 (61.8)	0.973	0.949-0.998	.032
Year of diagnosis					
2004	888 (45.6)	1058 (54.4)		Reference	
2005	856 (43.0)	1137 (57.0)	1.018	0.971-1.066	.466
2006	945 (42.7)	1269 (57.3)	1.027	0.982-1.073	.246
2007	1116 (41.8)	1556 (58.2)	1.029	0.986-1.074	.192
2008	1114 (38.9)	1753 (61.1)	1.054	1.011-1.099	.013
2009	1161 (37.3)	1952 (62.7)	1.055	1.012-1.099	.011
2010	1144 (34.6)	2164 (65.4)	1.077	1.036-1.121	<.001

(*continued on next page*)

Table 1 (*continued*)

Characteristic	PMRT		Multivariable prevalence ratio*	95% CI	*P* value
	No (n = 10,986)	Yes (n = 18,284)			
2011	1176 (32.2)	2476 (67.8)	1.094	1.053-1.137	<.001
2012	1197 (32.2)	2522 (67.8)	1.104	1.062-1.148	<.001
2013	1389 (36.7)	2397 (63.3)	1.086	1.044-1.130	<.001
Grade					
Missing	1029 (37.8)	1693 (62.2)			
Well differentiated	743 (36.8)	1279 (63.3)		Reference	
Moderately differentiated	3670 (34.7)	6893 (65.3)	1.022	0.994-1.050	.133
Poorly differentiated, undifferentiated, anaplastic	5544 (39.7)	8419 (60.3)	1.028	0.999-1.057	.059
Surgical margins					
Missing	237 (44.6)	295 (55.4)			
Negative	9871 (37.2)	16,690 (62.8)		Reference	
Positive	878 (40.3)	1299 (59.7)	0.964	0.936-0.992	.013
Laterality					
Missing	8 (27.6)	21 (72.4)			
Right	5403 (37.5)	8999 (62.5)		Reference	
Left	5575 (37.6)	9264 (62.4)	1.001	0.987-1.016	.848
TNM pathologic T category					
Missing	537 (41.4)	761 (58.6)			
ypT0-Tis	566 (40.0)	850 (60.0)		Reference	
ypT1-T2	6990 (37.7)	11,571 (62.3)	0.999	0.963-1.037	.956
ypT3-T4	2893 (36.2)	5102 (63.8)	1.016	0.977-1.056	.440
TNM pathologic N category					
ypN1	6692 (42.1)	9184 (57.9)		Reference	
ypN2	2872 (31.6)	6214 (68.4)	1.090	1.072-1.108	<.001
ypN3	1422 (33.0)	2886 (67.0)	1.084	1.061-1.109	<.001
Regional lymph nodes examined					
Missing	222 (43.1)	293 (56.9)			
<10	4162 (39.5)	6363 (60.5)		Reference	
10-50	6589 (36.2)	11,610 (63.8)	1.018	1.002-1.034	.030
>50	13 (41.9)	18 (58.1)	0.918	0.701-1.202	.533
Median	13	13			
Range	0-68	0-90			
Hormonal therapy					
Missing	682 (60.2)	451 (39.8)			
No	5524 (48.6)	5842 (51.4)		Reference	
Yes	4780 (28.5)	11,991 (71.5)	1.179	1.158-1.199	<.001
Immediate breast reconstruction					
No	8124 (37.2)	13,717 (62.8)		Reference	
Yes	2862 (38.5)	4567 (61.5)	0.967	0.949-0.985	<.001
Interval to chemotherapy from diagnosis (mo)					
Median	1.02	0.95			
Range	0-30.28	0-24.92			
Interval to mastectomy from diagnosis (mo)					
Median	5.92	5.88			
Range	2.63-33.33	2.70-29.36			

Abbreviations: CI = confidence interval; PMRT = postmastectomy radiation therapy.
Data presented as n (%), unless otherwise noted; row percentages might not sum to 100% because of rounding.
* Prevalence ratios (95% CIs and *P* values) computed from multivariable logistic regression model adjusted for all covariates included in Table 1.

Results

We identified 29,270 patients who fulfilled the study inclusion criteria. Of these patients, 18,284 (62.5%) had received PMRT (Fig. E1; available online at www.redjournal.org). The median age of the cohort was 51 years (range 19-90). Most patients were white (77.6%) and had Charlson-Deyo comorbidity scores of 0 to 1 (98.3%). Of the patients, 54% had ypN1 disease, 31.0% had ypN2 disease, and 14.7% had ypN3 disease. The PMRT usage rates among the ypN1,

ypN2, and ypN3 patients were 57.8%, 68.4%, and 67.0%, respectively. Among the patients who received PMRT, 72.5% also received regional nodal irradiation.

The baseline patient, facility, and tumor characteristics stratified by PMRT usage are listed in Table 1. Multiple factors independently associated with PMRT use were identified on multivariable analysis. Patients who received PMRT were more likely to be non-Hispanic and have lower Charlson-Deyo comorbidity scores (0 vs ≥2). Patients with non-Medicaid/Medicare insurance, those who lived closer to the reporting facility (≤50 vs >50 miles), patients treated at a comprehensive cancer or academic facility (vs a community practice), and those diagnosed in 2008 or later (vs 2004) were also more likely to receive PMRT. The tumor characteristics associated with increased PMRT use included increasing pathologic N category and a greater number of lymph nodes examined. Patients who received hormonal therapy were also more likely to receive PMRT; however, patients who had undergone immediate breast reconstruction were less likely to receive PMRT. Age (≤50 vs >50 years), race, median income quartile, grade, laterality, and pathologic T category were not significantly associated with PMRT use.

Overall, the PMRT usage rates increased during the study period, from 54.4% in 2004 to 63.3% in 2013. Table E1 (available online at www.redjournal.org) summarizes the patterns of PMRT usage stratified by the annual percentage of change (APC) for the overall cohort and by age, race, and facility location. For the overall cohort, a significant increase was seen in PMRT usage from 2004 to 2011 (APC 3.21; 95% CI 2.55-3.86). A similar trend was seen for patients aged <50 years (APC 3.84, 95% CI 3.17-4.50), white patients (APC 3.02, 95% CI 2.31-3.74), and black patients (APC 4.12, 95% CI 2.54-5.73).

After excluding those patients diagnosed after 2008 and those with incomplete follow-up data, 11,626 patients remained in the cohort for the survival analyses (Fig. E1; available online at www.redjournal.org). Multiple independent predictors of mortality were identified in the TDCRM model (Table 2). Older age, black race, higher Charlson-Deyo comorbidity score, higher grade disease, positive surgical margins, increasing pathologic T category, and increasing pathologic N category were associated with decreased survival. Patients with private insurance or managed care and those with a greater median income quartile had improved survival, as did patients who received hormonal therapy, those with a greater number of lymph nodes examined, and those who had undergone immediate breast reconstruction.

The effect of PMRT on OS was analyzed in the TDCRM and CPH models using a 12-month landmark from diagnosis for all patients and the ypN1, ypN2, and ypN3 subsets (Table 3). In both models, PMRT was not associated with improved survival for all patients, ypN1 patients, or ypN2 patients on multivariable analysis. For the ypN3 patients, PMRT was associated with improved survival in both the landmark CPH and the TDCRM models (multivariable HR 0.870, 95% CI 0.760-0.995; multivariable HR 0.848, 95% CI 0.744-0.967, respectively).

Of the entire cohort (n = 29,270), 1422 did not have a radiation dose code, 118 had a code for receipt of an unknown radiation dose, and 627 had a code for receipt of <45 Gy. Together, these patients accounted for 7.4% of the cohort. We restricted our PMRT group to patients receiving ≥45 Gy to the chest wall with or without regional lymph nodes to exclude patients who might have received palliative radiation therapy. Using this definition, 2% of the patients receiving <45 Gy were included in the no-PMRT group. Another 5% of patients were coded as having received radiation but without a specified dose; they were also included in the no-PMRT group. Because this categorization could have introduced a bias toward the null, we reran the TDCRM model in a sensitivity analysis that included these patients in the PMRT group, and the results were unchanged (Table E2; available online at www.redjournal.org).

The unadjusted Kaplan-Meier estimates of OS for all patients stratified by PMRT receipt using the CPH landmark data set are shown in Figure 1 and the adjusted HRs for PMRT among all patients and the ypN1, ypN2, and ypN3 subsets using the TDCRM model in Figure 2. PMRT was again associated with improved survival among the ypN3 patients only (HR 0.85, 95% CI 0.74-0.97). After adjusting for patient, facility, and tumor variables (Table 4), the 5-year OS rates were similar in the PMRT and no-PMRT groups for all patients (80% vs 80%; $P = .963$), ypN1 patients (77% vs 78%; $P = .377$), and ypN2 patients (76% vs 77%; $P = .220$). The adjusted 5-year OS rate was significantly greater in the PMRT group for the ypN3 patients (66% vs 63%; $P = .042$).

Discussion

In the present large national cancer registry–based retrospective analysis, we found that the overall PMRT usage rate for patients who received NAC and had pathologically positive lymph nodes at mastectomy increased from 54.4% in 2004 to 63.3% in 2013, with a significant increase in the APC from 2004 to 2011 ($P < .001$). Multiple factors, including non-Hispanic ethnicity, lower Charlson-Deyo comorbidity score, non-Medicaid/Medicare insurance, treatment at a comprehensive care or academic facility, a later year of diagnosis, and the absence of immediate breast reconstruction were associated with increased PMRT usage. Although patients with ypN2 and ypN3 disease were more likely to receive PMRT than were patients with ypN1 disease, the PMRT usage rates within both subgroups were only 68.4% and 67.0%, respectively.

In the survival analyses, younger age, nonblack race, lower Charlson-Deyo comorbidity score, private insurance, greater median income quartile, receipt of hormonal therapy, lower-grade disease, negative surgical margins, lower pathologic T and N categories, and a greater number of lymph nodes examined were independently associated with

Table 2 Association between baseline characteristics and overall mortality (n = 11,626) with multiple imputation

Characteristic	Multivariable HR*	95% CI	*P* value
Age (y)			
≤50		Reference	
>50	1.166	1.082-1.256	<.001
Race			
White		Reference	
Black	1.284	1.183-1.393	<.001
Other	0.811	0.677-0.973	.024
Hispanic ethnicity			
No		Reference	
Yes	0.903	0.797-1.023	.108
Charlson-Deyo comorbidity score			
0		Reference	
1	1.189	1.078-1.310	<.001
≥2	1.501	1.205-1.870	<.001
Primary payer			
Not insured		Reference	
Private insurance/managed care	0.800	0.696-0.920	.002
Medicaid/Medicare	1.051	0.911-1.213	.495
Other government insurance	1.009	0.741-1.374	.954
Median income quartile by zip code			
<$38,000		Reference	
$38,000-$47,999	0.966	0.865-1.078	.536
$48,000-$62,999	0.865	0.775-0.965	.010
≥$63,000	0.813	0.711-0.929	.003
Distance from the reporting facility (miles)			
≤50		Reference	
>50	0.869	0.770-0.979	.022
Facility type			
Community		Reference	
Comprehensive	0.970	0.857-1.098	.624
Academic	0.882	0.773-1.007	.063
Other	0.720	0.193-2.689	.625
Facility location			
Northeast		Reference	
South	0.961	0.875-1.057	.412
Central	1.011	0.913-1.119	.840
West	0.905	0.801-1.023	.110
Year of diagnosis			
2004		Reference	
2005	0.930	0.845-1.024	.138
2006	0.905	0.821-0.998	.046
2007	1.010	0.919-1.110	.830
2008	1.051	0.953-1.157	.319
Hormonal therapy			
No		Reference	
Yes	0.478	0.447-0.511	<.001
Grade			
Well differentiated		Reference	
Moderately differentiated	1.291	1.104-1.510	.001
Poorly differentiated, undifferentiated, anaplastic	1.929	1.655-2.248	<.001
Surgical margins			
Negative		Reference	
Positive	1.294	1.171-1.429	<.001
Laterality			
Right		Reference	
Left	1.006	0.948-1.067	.855

(*continued on next page*)

Table 2 (*continued*)

Characteristic	Multivariable HR*	95% CI	*P* value
TNM pathologic T category			
ypT0-Tis		Reference	
ypT1-T2	1.415	1.155-1.735	<.001
ypT3-T4	2.056	1.671-2.530	<.001
TNM pathologic N category			
ypN1		Reference	
ypN2	1.696	1.582-1.816	<.001
ypN3	2.433	2.241-2.642	<.001
Regional lymph nodes examined			
<10		Reference	
10-50	0.850	0.796-0.908	<.001
>50	0.821	0.388-1.738	.606
Immediate breast reconstruction			
No		Reference	
Yes	0.877	0.801-0.962	.005

Abbreviations: CI = confidence interval; HR = hazard ratio.
* HRs (95% CIs and *P* values) computed from multivariable logistic regression model adjusted for all covariates shown in Table 2.

improved survival. After adjustment for other covariates, PMRT was associated with improved survival for the ypN3 patients in both the time-dependent and the landmark analyses.

Our data provide important insights into the national PMRT practice patterns within this patient population during the previous decade. This is an area of increasing clinical relevance, because recently reported data have demonstrated that the use of preoperative systemic therapy in breast cancer is increasing (16). We observed statistically significant variations in the PMRT usage patterns in breast cancer patients treated with NAC, depending on the comorbidity score and disease stage. More notably, multiple socioeconomic factors, including ethnicity and insurance type, were independently associated with the receipt of PMRT after NAC. Previous studies using national cancer registry data showed similar associations between socioeconomic factors and different types of breast cancer treatment modalities, highlighting the importance of standardized care, not only in the setting of NAC, but also in all aspects of breast cancer management (17-19).

Although the benefits of PMRT in the setting of adjuvant chemotherapy have been demonstrated in multiple randomized trials and in the Early Breast Cancer Trialists' Collaborative Group meta-analysis (3-5), data from ongoing NAC trials have yet to mature (20, 21). It is unclear whether the indications for PMRT in the absence of NAC can be extrapolated to this setting, because NAC can lead to

Table 3 Univariable and multivariable hazard ratios for overall mortality stratified by PMRT (n=11,626) with multiple imputation

Variable	Univariable HR	95% CI	*P* value	Multivariable HR*	95% CI	*P* value
Overall						
CPH model with 12-mo landmark; n=11,254 (6284 vs 4970)	0.978	0.920-1.040	.4838	1.002	0.940-1.067	.9626
TDCRM model; n=11,626 (6726 vs 4900)	0.973	0.917-1.034	.3773	0.996	0.936-1.06	.9018
ypN1						
CPH model with 12-mo landmark; n=5921 (2914 vs 3007)	0.984	0.894-1.084	.7457	1.046	0.946-1.157	.3772
TDCRM model; n=6059 (3196 vs 2863)	1.003	0.912-1.103	.9531	1.064	0.964-1.175	.2143
ypN2						
CPH model with 12-mo landmark; n=3575 (2241 vs 1334)	0.921	0.831-1.021	.1186	1.069	0.961-1.190	.2195
TDCRM model; n=3710 (2396 vs 1314)	0.883	0.798-0.977	.0161	1.042	0.938-1.158	.4377
ypN3						
CPH model with 12-mo landmark; n=1758 (1036 vs 722)	0.759	0.669-0.862	<.0001	0.870	0.760-0.995	.0419
TDCRM model; n=1857 (1134 vs 723)	0.739	0.653-0.836	<.0001	0.848	0.744-0.967	.0137

Abbreviations: CI = confidence interval; CPH = Cox proportional hazards; HR = hazard ratio; PMRT = postmastectomy radiation therapy; TDCRM = time-dependent Cox regression model.
* Multivariable HR adjusted for age, race, ethnicity, Charlson-Deyo comorbidity score, primary payer, median income quartile by zip code, distance from reporting facility, facility type, facility location, year of diagnosis, hormonal therapy, grade, surgical margins, laterality, TNM pathologic T category, TNM pathologic N category, regional lymph nodes examined, and immediate breast reconstruction.

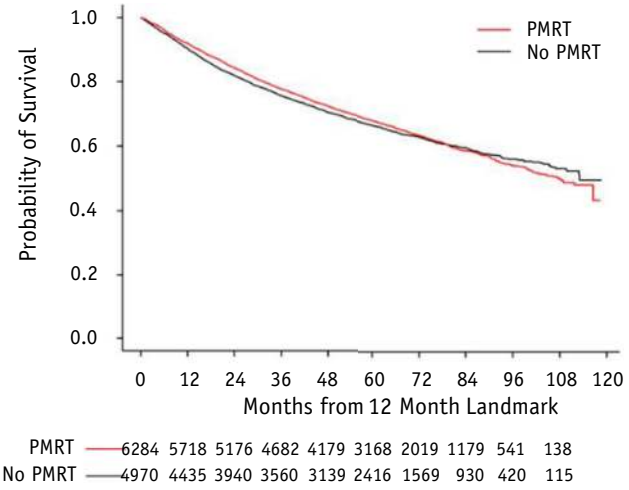

Fig. 1. Kaplan-Meier survival curves for all patients stratified by postmastectomy radiation therapy (PMRT) receipt using the 12-month landmark data set.

significant tumor downstaging (2). Without strong evidence to guide PMRT decision-making after NAC, the current National Comprehensive Cancer Network guidelines have recommended using the prechemotherapy tumor characteristics to determine adjuvant locoregional management (22).

In contrast, the available retrospective data have suggested that the postchemotherapy pathologic nodal stage can predict for LRR and therefore should be considered in the clinical decisions regarding PMRT. For example, Buchholz et al (7) found that pathologic involvement of ≥4 lymph nodes after NAC was independently associated with LRR (HR 2.7; $P=.008$). This observation was validated by Garg et al (23) in a similar analysis of patients clinically presenting with early-stage disease who had a large residual nodal disease burden. Another series by Huang et al (8) showed significant improvement in the 10-year LRR rate with the addition of PMRT in patients with ≥4 involved lymph nodes (59% vs

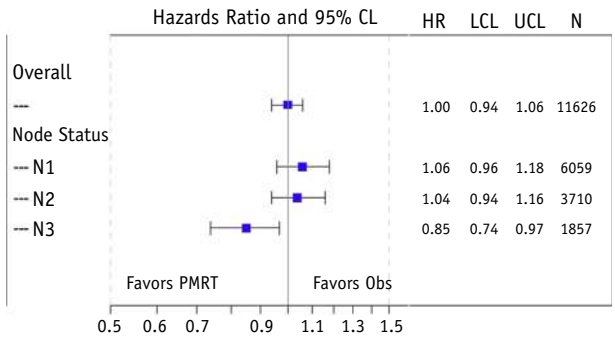

Fig. 2. Forest plot of the effect of postmastectomy radiation therapy (PMRT) on overall survival in all patients and stratified by each nodal subgroup. *Abbreviations:* CL = confidence limit; HR = hazard ratio; LCL = lower confidence limit; Obs = observation; UCL = upper confidence limit.

Table 4 Adjusted 2- and 5-year overall survival estimates by nodal stage using the CPH model with 12-month landmark

Variable	Deaths/Total (%)	Adjusted* 2-y OS (%; 95% CI)	Adjusted* 5-y OS (%; 95% CI)
Overall			
PMRT	3958/6284 (63)	91 (88-94)	80 (74-86)
No PMRT	3146/4970 (63)	91 (88-94)	80 (74-86)
ypN1			
PMRT	2163/3007 (72)	90 (85-95)	77 (67-87)
No PMRT	2105/2914 (72)	90 (85-95)	78 (68-88)
ypN2			
PMRT	1299/2241 (58)	88 (82-95)	76 (65-89)
No PMRT	749/1334 (56)	89 (83-95)	77 (66-89)
ypN3			
PMRT	496/1036 (48)	84 (72-98)	66 (47-96)
No PMRT	292/722 (40)	82 (69-98)	63 (41-95)

Abbreviations: CI = confidence interval; CPH = Cox proportional hazards; PMRT = postmastectomy radiation therapy; OS = overall survival.

* Estimates for patients with the following covariate risk factors: age ≤50 years, white race, non-Hispanic ethnicity, uninsured, income <$38,000, ≤50 miles from reporting facility, treatment at community facility, northeast location, diagnosed in 2004, no hormonal therapy, well-differentiated grade, negative surgical margins, right laterality, T0 category, <10 regional lymph nodes examined.

16%; $P<.0001$). Despite the available evidence supporting PMRT use for patients with a high nodal disease burden after NAC, the present analysis demonstrated that many ypN2 and ypN3 patients treated during the past decade did not receive PMRT.

The published data on the benefits of PMRT in patients with 1 to 3 pathologically positive lymph nodes after NAC are less clear. The previously cited series reported LRR rates of 10% to 20% in the absence of PMRT (7, 8), which were corroborated by the pooled analysis from the NSABP B-18 and B-27 trials (6). However, PMRT has not been shown to significantly improve local control in these patients (8). Conflicting results were seen in a recent NCDB analysis by Rusthoven et al (24) of patients presenting with clinical stage N1 disease, which showed improved OS with PMRT for all pathologic nodal subgroups (ypN0, ypN1, and ypN2-ypN3; $P<.05$ for all). The discrepancies between their analysis and ours can be attributed to the differing inclusion criteria and statistical methods used. Rusthoven et al (24) analyzed patients with upfront clinical stage N1 disease. In contrast, only 49% of patients had upfront clinical stage N1 disease in the present analysis. Approximately 15% of patients had clinically node-negative disease, 20% had clinical N2-N3 disease, and the clinical N stage was unknown for 16% of the patients. Because it can be challenging to accurately ascertain the upfront clinical stage, we believe our inclusion criteria might address a more practical clinical question. We also used a more rigorous statistical approach to address the missing data with the multiple imputation method (compared with analyzing the unknown values categorically). Finally,

although Rusthoven et al (24) used the propensity score matching method to analyze the relationship between PMRT and OS, we did not perform this analysis. Studies have shown that multivariable logistic regression modeling is the technique of choice when ≥8 events per confounder are present. The multivariable logistic regression empirical coverage probability increases as the number of events per confounder increases, and the propensity score empirical coverage probability decreases after ≥8 events per confounder (24, 25). With 4415 deaths and 18 confounders, we had much more than 8 events per confounder. Therefore, multivariable logistic regression was the optimal method for analyzing these data.

The optimal adjuvant locoregional management for patients with 1 to 3 positive lymph nodes remains an area of controversy, in both the setting of neoadjuvant chemotherapy and the setting of adjuvant chemotherapy. The lower national rate of PMRT usage within the ypN1 subset observed in the present analysis might have been a reflection of this ongoing controversy. It is likely that certain subsets within the 1- to 3-lymph node−positive population have a greater risk of LRR and thus might benefit from PMRT. Interest is increasing in considering tumor biology and the response to NAC to help identify such patients (26). Older series have even suggested that patients with less extensive locoregional disease and favorable tumor biology might derive a larger benefit from PMRT in the setting of adjuvant chemotherapy (27, 28). In the present analysis, it is possible that a survival benefit with PMRT was not seen for the ypN1 and ypN2 subsets because of advances in surgical techniques and systemic therapies in the modern era. Longer follow-up data might also be needed to observe a benefit in these lower risk subgroups.

Our study had several limitations. The NCDB does not contain all relevant treatment information that should be considered, such as the chemotherapy agents administered or the specific nodal regions targeted with radiation. Additionally, the only long-term endpoint available is OS, which was further limited in the present analysis by the relatively short follow-up period for breast cancer. Another endpoint of particular interest to our analysis was the LRR rate. Finally, the limitations inherent to national cancer registry data include both patient selection and institutional reporting bias. We also could not account for any errors in reporting or coding. Although we attempted to address the issue of missing data using multiple imputation analysis, this also assumes that the incomplete data were missing at random. However, using the NCDB, we were able to analyze a very large and homogeneous patient cohort. This is noteworthy, because our results have corroborated the findings from previous smaller series.

Conclusions

We report the PMRT patterns and the effect of PMRT on OS in patients treated with NAC and mastectomy with residual pathologic nodal disease. We found that PMRT was underused in patients with advanced pathologic ypN3 nodal disease who might derive a survival benefit from treatment. We also identified multiple independent socioeconomic disparities in national PMRT usage.

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